# Five factors to consider when scaling up biologics production to meet global commercial output

Bioreactor scale-up is a critical step in the production of biologics such as therapeutic proteins, monoclonal antibodies (mAbs), and vaccines. Scaling up can be complex; it requires choosing the optimal media formulations and securing reliable supply chains, while maintaining product quality and remaining cost-effective. While there are several critical parameters to consider, we have outlined the top five media-related factors to help you meet your global commercial output.

## Quality of raw materials

As impurities in raw materials can be amplified during the scale-up process, the quality of your raw materials should be a primary focus when scaling up. Formulations that work at bench scale are often not as productive when you begin to scale up to large bioreactors. Impurities can impact performance parameters (overall titers, growth of the cells, consistency, etc.), resulting in variable product performance and batch fluctuations. However, if you are having trouble scaling up, process analytics can highlight potential problems—e.g., trace elements within raw materials adding to contamination. Over the last few years, the analysis of raw materials has been a growing focus within the bioprocessing industry, with analytical techniques such as chromatography, spectroscopy, and mass spectrometry used to characterize raw materials, depending on a drug developer's specific needs.

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High-quality raw materials are also essential for maintaining the critical quality attributes of your biologic—defined during early-stage development—as you scale up. A deviation in these attributes can change a protein's biological activity, which can prevent a biologic from getting to, or staying at, market.

Scale-up is predominantly focused on maintaining high-quality yields, so optimizing protein quality is key. Glycosylation, a critical posttranslational modification to proteins, can fluctuate during scale-up, leading to protein aggregation and insolubility. Maintaining this balance can be a challenge; however, process optimization, trace element analysis, and the introduction of supplements such as peptones, animal origin–free (AOF), and/or chemically defined (CD) components, can all be used to improve performance or maintain productivity at larger volumes.

### Cost of goods (COGS)

When scaling up to meet global commercial output, it is important to consider the cost of goods sold (COGS) associated with your process, and how COGS can vary with scale. COGS considerations can also contribute to the decision to discontinue a biologic's development, so efforts must be made to establish a cost-effective process as soon as you start to scale up.

Technologies or process improvements—such as single-use technologies, perfusion processes to replace fed-batch processes, continuous chromatography, and end-to-end continuous processes—are all helping to reduce COGS in bioprocessing applications [1]. Process improvements in the mAb sector over the last 40 years have already reduced the COGS associated with process manufacturing and development considerably—from $1,000–10,000 per gram in the 1980 to 1990s, to $10–100 per gram at present [1].

COGS might also be reduced if a formulation is optimized early on, limiting the number of failed batches and wasted material associated with process development. While this is easier said than done, choosing an outsourcing partner who can assist you in optimizing your process may help. Outsourcing the storage of raw materials also has the potential to reduce COGS; storage in-house may lead to increased product waste, as products pass their expiration date.

Process modifications can also reduce overall COGS by improving productivity. This could be through switching to a perfusion process to improve bioreactor productivity or switching from liquid to powder media to save on shipping costs. But wherever you are purchasing your process components, you will also want to make sure the supplier has stable cost structuring. Evaluating process modeling, economics, and optimization can help you estimate COGS and outline how to optimize procurement and manufacturing processes.

### Manufacturing footprint and outsourcing

Considering your in-house manufacturing footprint is important when scaling up. For instance, liquid cell culture media can be ideal at the preclinical stage, but when it comes to scaling up, dehydrated media in the form of dry powder may improve the logistical scalability of a process (in terms of cost, shipping, and in particular storage space). Recent advances in milling technologies are helping to bridge the gap between liquid media and conventional dried powder, offering a powdered media with improved consistency and additional benefits—including faster dissolution, minimal dust generation, and quicker preparation times.

With just-in-time delivery, resources arrive exactly when you need them, so you don't have to waste floor space storing large quantities of liquids or powders, or personnel time.

It is also important to identify whether you actually have the capacity to manufacture your bulk process liquids in-house, or whether outsourcing might benefit your processes. Large-scale biopharmaceutical production facilities can devote as much as 20% of their floor space to dry powder media and their preparation [2], which can have a major impact on operations and costs. Often, biopharmaceutical developers outsource the production of their bulk process liquids—including production media—to a supplier, or even multiple suppliers. Having a primary, secondary, and even tertiary supply of bulk process liquids is not uncommon in the industry in order to reduce any risk associated with supply chain instability. In addition, this helps to ensure that your supplier will have the raw materials on hand to meet your large-scale commercial manufacturing needs.

By outsourcing media production, you can save space and time. With just-in-time delivery, resources arrive exactly when you need them, so you don't have to waste floor space storing large quantities of liquids or powders, or personnel time. This enables you to use the facility space you've saved to manufacture your valuable product rather than storing process materials.

Outsourcing can also save costs, allowing you to purchase larger quantities of media than could be produced in-house and perform fewer QC tests on these large batches of material. Ultimately, these are important considerations during scale-up, as outsourcing has the potential to significantly improve operational efficiency.

## The regulatory landscape

Speed-to-market is an important consideration, but without properly considering the regulatory landscape, your biologic may never get to market.

The first step is making sure that you have the correct traceability documentation for each individual component used in the formulation. Using approved and traceable raw materials, delivered with full regulatory documentation, can help your biologic move smoothly through the approval process.

Successful process characterization is key to driving faster progression to regulatory approval, and ultimately, bringing your biologic to market faster. Drug makers are required to conduct clinical trials to demonstrate that a biologic is safe and effective; the FDA also scrutinizes manufacturing plants to ensure that therapeutics are consistent from batch to batch [3]. cGMP regulations require that all commercially produced biologics meet stringent assay, quality, and purity requirements. When scaling up, the production of a biologic must be optimized to meet regulatory requirements while still making sure it is cost-effective and reproducible.

However, nuances between different regulatory bodies cannot be overlooked, and regulations differ country by country. A formulation has to be independently approved by each country, as clinical data cannot be leveraged globally. An awareness of any changes during scale-up is critical, as these changes can impact the final formulation as well as its approval.

## Unpredictability and preparedness

It's hard to properly consider or even plan for unpredictability, but it's a factor that should be addressed when scaling up production of a biologic.

Consider disasters during your scale-up plans—what would happen if there was a global shortage of a product?

Could a manufacturing partner help? Choose suppliers with increased redundancy, a global footprint, and multi-sourced materials. Media manufacturers often hold safety stocks of raw materials so that you can have access to media even during times of crisis. By planning for the unpredictable, you should be able to maintain quality and keep costs down, even if major disruptions threaten your manufacturing processes.

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## Putting it all together

There are a number of factors to consider when scaling up your bioprocess. In an industry under extreme pressure due to tight timelines, numerous suppliers, and limited budgets, getting these factors right early on is crucial. One option to accelerate your path through scale-up is to partner with a supplier who can tackle this list for you. Partnering with a supplier whose key capabilities are scale-up, optimization, analytics, supply, and logistics helps you focus on your core capabilities—getting your biologic to the people who need it.

Regardless of how you successfully scale up production of your biologic, there are a number of factors to consider. With these factors taken into consideration, you will be well on your way to seamlessly scaling up your new discovery.

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